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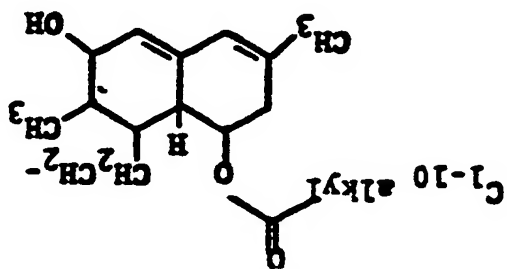
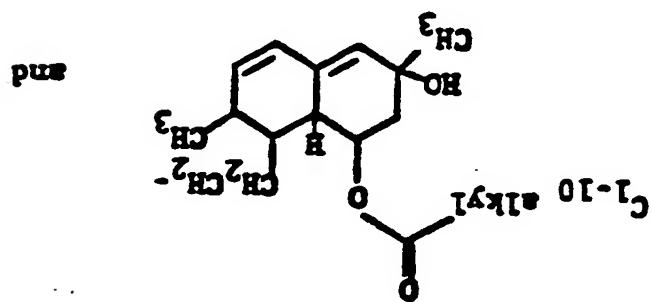
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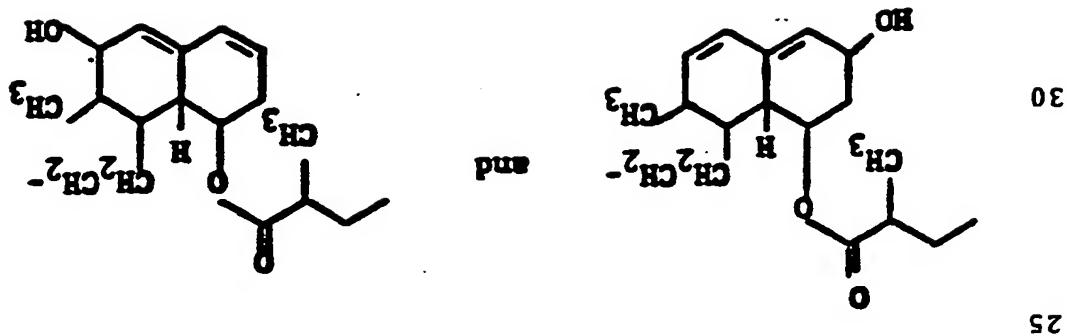
- 3 -

2212S/0985A

U.S. Patent 4,517,373 discloses semi-synthetic compounds represented by the above general formula wherein R is



U.S. Patent 4,346,227 and U.S. Patent 4,448,979 also disclose semi-synthetic compounds represented by the above general formula wherein R is



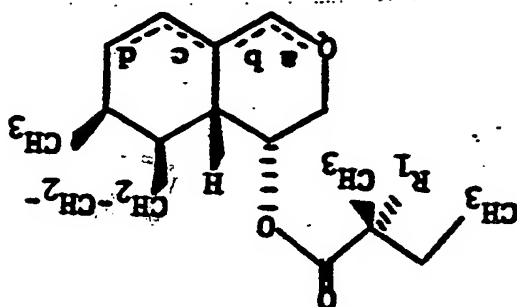
0245003

The naturally occurring compounds and their semi-synthetic analogs have the following general structural formulae:



wherein: Z is hydrogen, C₁₋₅ alkyl or C₁₋₅ alkyl substituted with a member of the group consisting of phenyl, dimethylamino, or acetylamino;

15 R is:



wherein Q is R₂-C(=O)-CH₃ or R₂-CH₂-OH; R₂ is H or OH;

R₁ is hydrogen or methyl; and a, b, c, and d represent optional double bonds, especially where b and d represent double bonds or a, b, c, and d are all single bonds.

#5

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EUROPEAN PATENT APPLICATION

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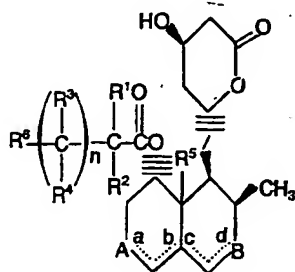
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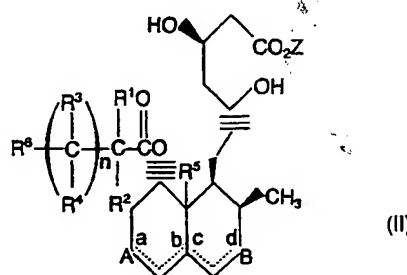
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54 Antihypercholesterolemic compounds.

57 Novel 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors which are useful as antihypercholesterolemic agents and are represented by the following general structural formulae (I) and (II):



(I)



(II)

and pharmaceutically acceptable salts of the compounds (II) in which Z is hydrogen are disclosed.

EP 0 245 003 A2

AMY

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- 1 - 17377Y

TITLE OF THE INVENTION

ANTIHYPERCHOLESTEROLEMIC COMPOUNDS

BACKGROUND OF THE INVENTION

5 Hypercholesterolemia is known to be one of
the prime risk factors for ischemic cardiovascular
disease such as arteriosclerosis. To date, there is
still no effective antihypercholesterolemic agent
commercially available that has found wide patient
10 acceptance. The bile acid sequestrants seem to be
moderately effective but they must be consumed in
large quantities, i.e. several grams at a time and
they are not very palatable.

 There are agents know, however, that are
15 very active antihypercholesterolemic agents that
function by limiting cholesterol biosynthesis by
inhibiting the enzyme, HMG-CoA reductase. These
agents include the natural fermentation products
compactin and mevinolin and a variety of semi-
20 synthetic and totally synthetic analogs thereof.

in which R_7 is hydrogen or methyl and R_8 is
 C_{1-10} alkyl, C_{1-10} CF_3 substituted alkyl,
 phenyl- C_{1-3} alkyl or substituted phenyl- C_{1-3} alkyl
 in which the substituent is halo, C_{1-3} alkyl or
 5 C_{1-3} alkoxy.

SUMMARY OF THE INVENTION

This invention relates to novel compounds
 which are HMG-CoA reductase inhibitors and are useful
 10 as antihypercholesterolemic agents. Specifically,
 the compounds of this invention are semi-synthetic
 analogs of compactin, mevinolin, hydroxylated
 compactin and hydroxylated mevinolin, and the dihydro
 and tetrahydro analogs thereof which possess a
 15 specifically substituted 8'-ester acyl moiety.
 Additionally, pharmaceutical compositions of these
 novel compounds, as the sole therapeutically active
 ingredient, and in combination with bile acid
 sequestrants are disclosed.

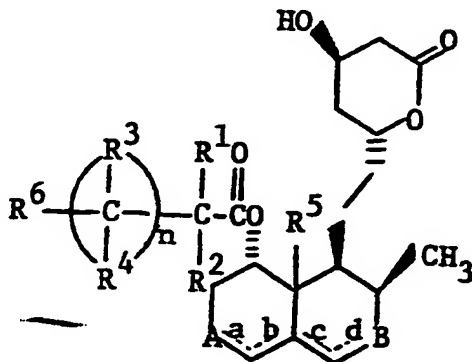
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DETAILED DESCRIPTION OF THE INVENTION

The specific HMG-CoA reductase inhibitors of
 this invention are the compounds represented by the
 following general structural formulae (I) and (II):

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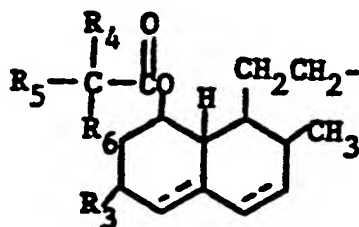


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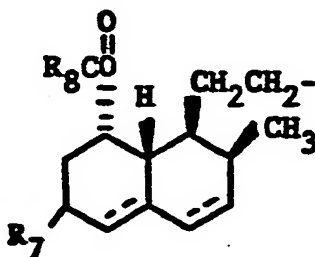
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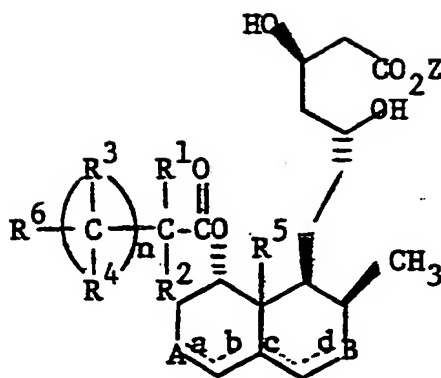
Japanese unexamined patent application
J59-122,483-A discloses a semi-synthetic compound
represented by the above general formula wherein R is



in which R_3 is hydrogen or methyl; R_4 is
hydrogen, halogen or haloalkyl; R_5 is hydrogen,
halogen or lower alkyl and R_6 is halogen, N_3 ,
hydroxy, thio, amino, loweralkoxy, lower alkylthio
and aralkylthio.

U.S. Patent 4,444,784 discloses 8'-acyloxy
derivatives of compactin, mevinolin and the dihydro
and tetrahydro analogs thereof. Generically
disclosed are the compounds represented by the above
general formula wherein R is:





20 wherein:

n is 0 to 5;

R¹ is C₁₋₃ alkyl;

R² is hydrogen or C₁₋₃ alkyl;

R³ and R⁴ independently are hydrogen C₁₋₃ alkyl,

25 C₃₋₇ cycloalkyl, phenyl or substituted phenyl in which the substituents are X and Y and when n is 2 to 5, each of the R³s and R⁴s are independently hydrogen, C₁₋₃ alkyl, C₃₋₇ cycloalkyl or only one of the

30 R³s and R⁴s are phenyl or substituted phenyl;

R^5 is hydrogen or hydroxy;

R^6 is selected from the group consisting of

- 5 a) $R^{15} \overset{\text{O}}{\parallel} \text{OC}$ in which R^{15} is hydrogen or C_{1-3} alkyl,
- b) $R^{16} R^{17} \overset{\text{O}}{\parallel} \text{NC}$ in which R^{16} and R^{17} independently are hydrogen or C_{1-3} alkyl or R^{16} and R^{17} together with the
- 10 nitrogen atom to which they are attached form a heterocycle selected from piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or thiomorpholinyl, and

- 15 c) $R^{18} \overset{\text{(O)}}{\underset{!}{\text{S}}}^q$ in which q is 0 to 2 and R^{18} is hydrogen, C_{1-5} alkyl, phenyl, and substituted phenyl wherein the substituents are X and Y;

20 A is $R^7 \overset{|}{\underset{\text{CH}_3}{\text{C}}}$ -or $R^7 \overset{|}{\underset{|}{\text{CH}}}$ in which R^7 is hydrogen or hydroxy;

B is $\overset{|}{\text{CHR}}^8$ which R^8 is hydrogen or hydroxy;

25 and

a, b, c and d represent single bonds, one of a, b, c or d represents a double bond, or both a and c or both b and d represent double bonds provided that when a is a double bond, A is

30 $\overset{\diagup}{\text{C}}=$ or $\text{CH}=$ and when d is a double bond, B is $\overset{\text{CH}_3}{\underset{|}{\text{C}}}=\text{CH}$; and

X and Y independently are hydrogen, halogen, trifluoromethyl, C₁₋₃ alkyl, nitro, cyano or a group selected from:

- 5 a) $R^9O(CH_2)_m$ in which m is 0 to 3 and R⁹ is hydrogen, C₁₋₃ alkyl or hydroxy-C₁₋₃ alkyl;
- 10 b) $R^{10}\overset{O}{\parallel}CO(CH_2)_m$ or $R^{10}\overset{O}{\parallel}OCO(CH_2)_m$ in which R¹⁰ is hydrogen, alkyl, hydroxy-C₂₋₃ alkyl, phenyl, naphthyl, amino-C₁₋₃ alkyl, C₁₋₃ alkylamino-C₁₋₃ alkyl, di(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, hydroxy-C₂₋₃ alkylamino-C₁₋₃ alkyl or di(hydroxy-C₂₋₃ alkyl)amino-C₁₋₃ alkyl;
- 15 c) $R^{11}\overset{O}{\parallel}OC(CH_2)_m$ in which R¹¹ is hydrogen, C₁₋₃ alkyl, hydroxy-C₁₋₃ alkyl, C₁₋₃ alkoxy-C₁₋₃ alkyl, phenyl or naphthyl;
- 20 d) $R^{12}R^{13}N(CH_2)_m$, $R^{12}R^{13}\overset{O}{\parallel}NC(CH_2)_m$ or $R^{12}R^{13}\overset{O}{\parallel}NCO(CH_2)_m$ in which R¹² and R¹³ independently are hydrogen, C₁₋₃ alkyl, hydroxy-C₂₋₃ alkyl or together with the nitrogen atom to which they are attached form a heterocycle group selected from piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl or thio-
- 25
- 30 morpholinyl;

e) $R^{14}S(O)_p(CH_2)_m$ in which p is 0 to 2 and R^{14} is hydrogen, C_{1-3} alkyl, amino, C_{1-3} alkylamino or di(C_{1-3} alkyl)-amino;

5 Z is hydrogen, C_{1-5} alkyl or C_{1-5} alkyl substituted with a member of the group consisting of phenyl, dimethylamino or acetylamino;

and pharmaceutically acceptable salts of the
10 compounds of the formula (II) in which Z is hydrogen.

Illustrative of one embodiment of this invention are the compounds of the formulae (I) and (II) wherein R^5 is hydrogen, R^7 is hydrogen, R^8 is hydrogen, a, b, c and d represent single bonds or
15 both b and d represent double bonds, R^1 is methyl, R^2 is methyl, and R^3 and R^4 are hydrogen. Specific

compounds are those compounds wherein R^6 is $R^{15} \overset{O}{\parallel} OC$.

Exemplifying this embodiment are the following
20 compounds:

- (1) 6(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 25 (2) 6(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-carbonylpropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and their corresponding free hydroxy acids.

30 Illustrative of a second embodiment of this invention are the compounds of the formulae (I) and (II) wherein R^5 is hydrogen, R^7 is hydrogen,

R^8 is hydrogen, a, b, c and d represent single bonds or both b and d represent double bonds, R^1 is methyl, R^2 is methyl, and R^3 and R^4 are hydrogen. Specific compounds are those compounds

5

wherein R^6 is $R^{16}R^{17}\overset{O}{\parallel}NC$. Exemplifying this embodiment are the following compounds:

(1) 6(R)-[2-[8(S)-[3-(diethylamino)-2,2-dimethyl-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,-
10 7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

(2) 6(R)-[2-[8(S)-(2,2-dimethyl-3-morpholino-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,-
6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-
15 hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

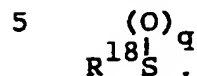
(3) 6(R)-[2-[8(S)-[3-(dimethylamino)-2,2-dimethyl-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,-
7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
3,4,5,6-tetrahydro-2H-pyran-2-one;

(4) 6(R)-[2-[8(S)-[4-(dimethylamino)-2,2-dimethyl-4-oxobutanoyloxy]-2(S),6(R)-dimethyl-1,2,6,-
7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
3,4,5,6-tetrahydro-2H-pyran-2-one;

(5) 6(R)-[2-[8(S)-[2,2-dimethyl-3-(methylamino)-3-oxopropionyloxy]-2(S),6(R)-dimethyl-
25 1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; and
their corresponding free hydroxy acids.

Illustrative of a third embodiment of this
30 invention are the compounds of the formulae (I) and (II) wherein R^5 is hydrogen, R^7 is hydrogen, R^8

is hydrogen, a, b, c and d represent single bonds or both b and d are double bonds, R^1 is methyl, R^2 is methyl, and R^3 and R^4 are hydrogen. Specific compounds are those compounds wherein R6 is



Exemplifying this embodiment are the following compounds:

(1) 6(R)-[2-[8(S)-[2-methyl-2-(methylthio)-
10 propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one;

(2) 6(R)-[2-[8(S)-[2-methyl-2-(methyl-
sulfinyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,-
15 7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-
hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

(3) 6(R)-[2-[8(S)-[2-methyl-2-(methyl-
sulfonyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,-
7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
20 3,4,5,6-tetrahydro-2H-pyran-2-one;

(4) 6(R)-[2-[8(S)-[2-methyl-2-(phenylthio)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one; and

25 (5) 6(R)-[2-[8(S)-[2-methyl-2-(phenyl-
sulfinyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a
(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one; and the corresponding free
hydroxy acid thereof.

Another embodiment of this invention is the class of compounds of the formula (II) wherein Z is hydrogen or C₁₋₅ alkyl and pharmaceutically acceptable salts of the compounds of the formula (II) wherein Z is hydrogen.

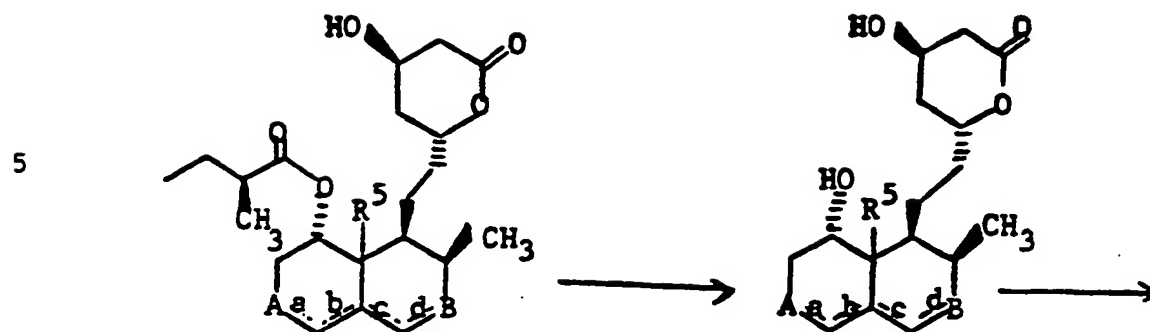
The pharmaceutically acceptable salts of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

The compounds of formula (I) are conveniently prepared from compactin, mevinolin, or the appropriate dihydro or tetrahydro analog thereof via the following general synthetic pathway:

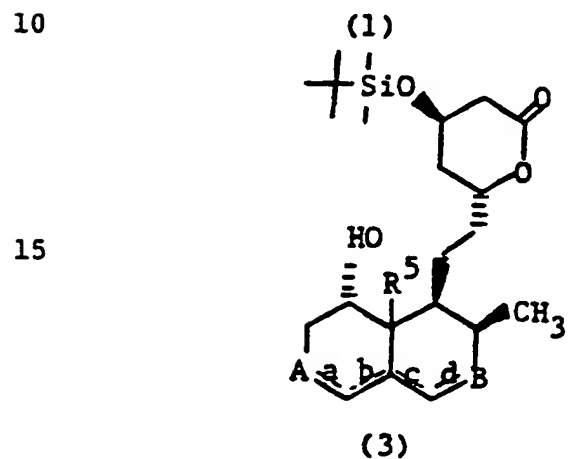
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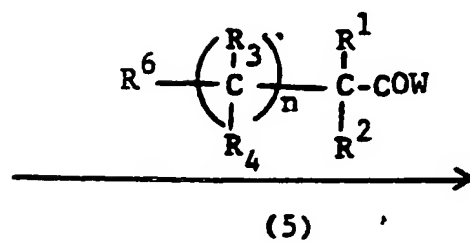
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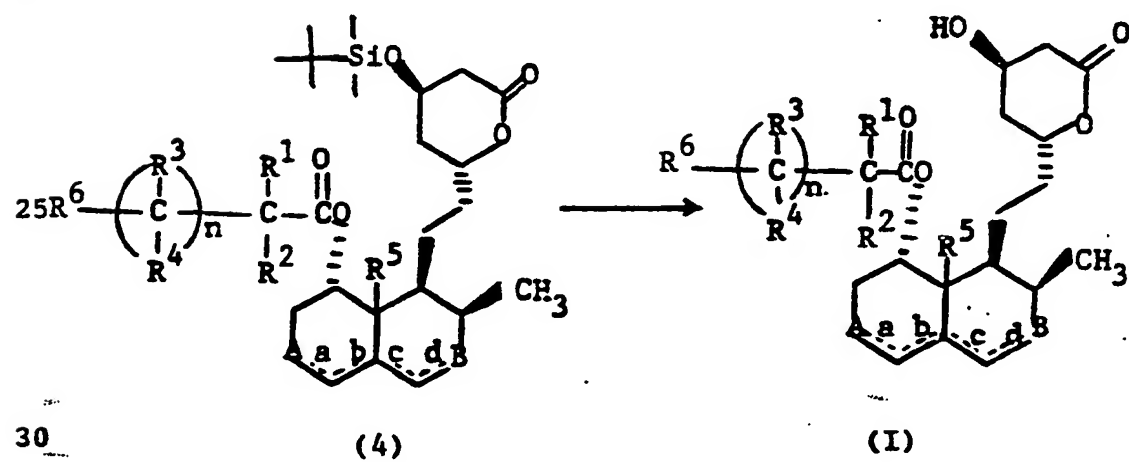
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The starting materials compactin, mevinolin, and their dihydro and tetrahydro analogs are readily available or may be prepared according to fermentation procedures disclosed in U.S. Patent 3,983,140, 5 U.S. Patent 4,049,495, U.S. Patent 4,231,938, U.S. Patent 4,294,846, and U.S. Patent 4,343,814, and the hydrogenation procedures disclosed in U.S. Patent 4,351,844. The appropriate starting material of formula (1) is then hydrolyzed under the conditions 10 disclosed in U.S. Patent 4,444,784 to afford the compounds of formula (2). The 4-hydroxy function in the lactone moiety of the compounds of formula (2) is protected with a suitable protecting agent, exemplified here as a dimethyl-t-butylsilyl group, 15 according to the procedure disclosed in U.S. Patent 4,444,784. Acylation of the 8'-hydroxy group of the compounds of the formula (3) is accomplished under suitable conditions utilizing the appropriately substituted acids or acid halides of the formula (5) 20 wherein n , R^1 , R^2 , R^3 , and R^4 are as described above, except that when R^6 contains a hydroxyl group that group is protected with a suitable protecting group, such as a trialkylsilyl group and W is hydroxyl or halogen. The protecting groups of the compound of 25 the formula (4) are removed utilizing suitable conditions to afford the compounds of the formula (I). For the compounds of this invention wherein the polyhydronaphthyl moiety is substituted with a hydroxy group, the compound of the Formula (4) is subjected 30 to a microbiological hydroxylation after the removal of the protecting groups utilizing the general

procedures disclosed in U.S. Patent 4,346,227, U.S. Patent 4,448,979, U.S. Patent 4,517,373 and Japanese Patent Application J-60-130,548.

5 The appropriately substituted acids and acid halides of the formula (5) are commercially available or prepared from known starting materials utilizing standard chemical transformations.

10 The compounds of the formula (II) wherein Z is hydrogen or a pharmaceutically acceptable salt thereof are readily prepared by the mild basic hydrolysis of the lactone moiety of the compounds of formula (I), careful acidification and formation of the appropriate salt utilizing standard procedures.

15 The compounds of the formula (II) wherein Z is C₁₋₅ alkyl or a substituted C₁₋₅ alkyl may be conveniently prepared by the procedures described in U.S. Patent 4,342,767.

20 The compounds of this invention are useful as antihypercholesterolemic agents for the treatment of arteriosclerosis, hyperlipidemia, familial hypercholesterolemia and the like diseases in humans. They may be administered orally or parenterally in the form of a capsule, a tablet, an injectable preparation or the like. It is usually desirable to
25 use the oral route. Doses may be varied, depending on the age, severity, body weight and other conditions of human patients but daily dosage for adults is within a range of from about 2 mg to 2000 mg (preferably 5 to 100 mg) which may be given in two to
30 four divided doses. Higher doses may be favorably employed as required.

The compounds of this invention may also be coadministered with pharmaceutically acceptable nontoxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastro-intestinal tract. Examples of such polymers include cholestyramine, colestipol and poly[methyl-(3-trimethylaminopropyl)imino-trimethylene dihalide]. The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15,000.

The intrinsic HMG-CoA reductase inhibition activity of the claimed compounds is measured in the in vitro protocol published in J. Med. Chem., 28, p. 347-358 (1985) and described below:

15 Isolation of HMG-CoA Reductase

Male Holtzman Sprague-Dawley rats (225-250 g) were kept on reversed lighting and fed Purina rat chow containing 3% cholestyramine for 7 days preceding their sacrifice by CO₂ asphyxiation. Livers were removed 6 hours into the dark cycle and used immediately to prepare microsomes. HMG-CoA reductase was solubilized from the freshly prepared microsome by the method of Heller and Shrewsbury [J. Biol. Chem., 1976, 251, 3815] and purified through the second ammonium sulfate precipitation step as described by Kleinsek et al., [Proc. Natl. Acad. Sci USA, 1977, 74, 1431]. The enzyme preparation was tested for HMG-CoA reductase potency and diluted with 100 mM phosphate buffer (pH 7.2) so that 100 ml of the enzyme solution, when added to the assay control, gave a value of 50,000-60,000 dpm. The enzyme preparation was stored at -80°C.

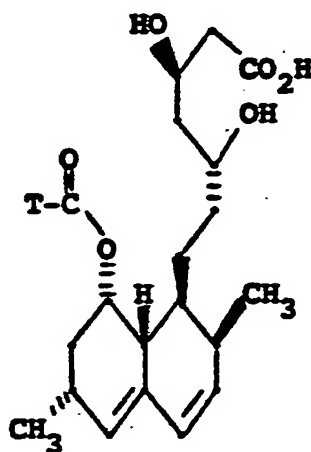
HMG-CoA Reductase Inhibition Assay

The assay is essentially the procedure of Shefer et al. [J. Lipid Res., 1972, 13, 402]. The complete assay medium contained the following in a total volume of 0.8 ml: phosphate buffer, pH 7.2, 100mM; MgCl_2 , 3 mM; NADP, 3 mM; glucose 6-phosphate, 10 mM; glucose-6-phosphate dehydrogenase, 3 enzyme units; reduced glutathione, 50 mM; HMG-CoA (glutaryl-3- ^{14}C , New England Nuclear), 0.2 mM (0.1 μCi); and partially purified enzyme stock solution, 100 μL .

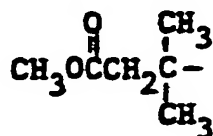
Test compounds or compactin (after first being converted to the sodium salt of their dihydroxy acid form in situ by addition of 1N NaOH (1 equivalent)) were added to the assay system in 10-mL volumes at multiconcentration levels. After a 40-minute incubation at 37°C with shaking and exposure to air, the reaction was stopped by the addition of 0.4 mL of 8N HCl. After an additional 30-minute incubation at 37°C to ensure the complete lactonization of mevalonic acid to mevalonolactone, 0.2 ml of the mixture was added to an 0.5 x 5.0 cm column containing 100-200 mesh BioRex 5, chloride form (Bio-Rad), wetted with distilled water, as described by Alberts et al., [J. Proc. Natl. Acad. Sci. U.S.A., 1980, 77, 3957]. The unreacted [^{14}C]HMG-CoA was absorbed on the resin and the [^{14}C] mevalonolactone was eluted with distilled water (2 x 1 ml) directly into 7-ml scintillation vials. Five milliliters of Aquasol-2 (New England Nuclear) was added to each vial, and radioactivity

was measured in a Packard Tri Carb Prias scintillation counter. IC_{50} value were determined by plotting percentage inhibition against test compound concentration and fitting a straight line to the resulting data by using the least-squares method. For estimation of relative inhibitory potencies, compactin was assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously.

Representative of the intrinsic HMG-CoA reductase inhibitory activities of the claimed compounds, tabulated below for a number of the claimed compounds are the relative potencies for said compounds.

TABLE 1

T

Relative Potency¹**87**

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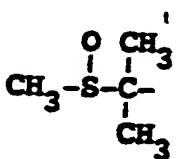
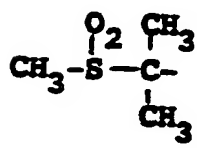
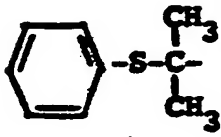
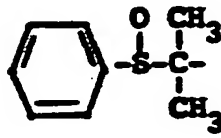
	<u>T</u>	<u>Relative Potency</u> ¹
5	$ \begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ \text{CH}_3\text{OC}-\text{C}- \\ \\ \text{CH}_3 \end{array} $	59
10	$ \begin{array}{c} \text{OCH}_3 \\ \parallel \\ (\text{CH}_3\text{CH}_2)_2\text{NCC}- \\ \\ \text{CH}_3 \end{array} $	22
15	$ \begin{array}{c} \text{OCH}_3 \\ \parallel \\ \text{O} \quad \text{NCC}- \\ \parallel \quad \\ \text{CH}_3 \end{array} $	20
20	$ \begin{array}{c} \text{OCH}_3 \\ \parallel \\ (\text{CH}_3)_2\text{NCC}- \\ \\ \text{CH}_3 \end{array} $	34
25	$ \begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ (\text{CH}_3)_2\text{NCCH}_2\text{C}- \\ \\ \text{CH}_3 \end{array} $	16
30	$ \begin{array}{c} \text{HO} \quad \text{CH}_3 \\ \parallel \quad \\ \text{CH}_3\text{NC}-\text{C}- \\ \\ \text{CH}_3 \end{array} $	13
	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{S}-\text{C}- \\ \\ \text{CH}_3 \end{array} $	200

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	<u>T</u>	<u>Relative Potency</u> ¹
5		13
10		22
15		156
20		38
25		

30 ¹ Relative to compactin which was arbitrarily assigned a value of 100.

Included within the scope of this invention is the method of treating arteriosclerosis, familal hypercholesterolemia or hyperlipidemia which comprises administering to a subject in need of such treatment
5 a nontoxic therapeutically effective amount of the compounds of formulae (I) or (II) or pharmaceutical compositions thereof.

The following examples illustrate the preparation of the compounds of the formulae (I) and
10 (II) and their incorporation into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

15

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25

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EXAMPLE 1

Preparation of 6(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

(a) Methyl 2,2-dimethylmalonate (1a)

To a stirred solution of dimethyl 2,2-dimethylmalonate (22.1 g, 138 mmol) in methanol (40 ml) at ambient temperature was added dropwise a solution of sodium hydroxide (5.52 g, 138 mmol) in water (20 ml). The reaction mixture was stirred for about 16 hours and then concentrated in vacuo at ambient temperature. The aqueous residue was cooled to 0-5°C and acidified with 6N hydrochloric acid. The aqueous mixture was saturated with sodium chloride and extracted with diethyl ether (2 x 150 ml). The combined extracts were washed with saturated aqueous sodium chloride (2 x 100 ml), dried over magnesium sulfate and concentrated in vacuo to give a colorless oil. The oil was purified by distillation at 15 mmHg to give the desired product which solidified on cooling. m.p. 35-8°C.

NMR(CDCl₃) δ =1.50 (6H, s), 3.78 (3H, s).

25 b) Methyl 2,2-dimethylmalonylchloride (1b)

To a stirred solution of the compound (1a) (5.0 g, 34.2 mmol) in dry benzene (25 ml) and dimethylformamide (2 drops) at ambient temperature was added oxalyl chloride (3.73 ml, 42.8 mmol). The reaction mixture was stirred for about 2 hours and the solvent removed in vacuo. The desired product

was distilled at reduced pressure to yield a colorless liquid. b.p. 61-2°C at 15 mmHg.

NMR(CDCl₃) δ =1.56 (6H, s), 3.80 (3H, s).

- 5 (c) 6(R)-[2-[8(S)-(2,2-Dimethyl-3-methoxy-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-ethyl]-4(R)-(dimethyl-tert-butylsilyloxy) 3,4,5,6-tetrahydro-2H-pyran-2-one
10 (1c)
-

- To a stirred solution of 6(R)-[2-[8(S)-hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-tert-butyldimethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-one (2.17 g, 5.0 mmol)
15 in dry pyridine (25 ml) was added 4-pyrrolidino-pyridine (148 mg, 1 mmol) and the reaction mixture under nitrogen was heated to 100°C. To the stirred reaction mixture at 100°C was added the compound (1b) (1.64 g, 10 mmol). After 4 hours, additional compound
20 (1b) (1.64 g, 10 mmol) was added. After 12 hours, the reaction mixture was allowed to cool to ambient temperature. The pyridine solvent was removed in vacuo and the residue suspended in diethyl ether (200 ml). The mixture was washed with water (50 ml)
25 containing 3N hydrochloric acid (10 ml), saturated aqueous sodium bicarbonate (25 ml) and saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to give a viscous oil. The oil was chromatographed on a 5 x 15
30 cm column of silica gel eluted with 50 percent diethyl ether/hexane to afford the des red product

and a minor amount of the compound (1a) as a semisolid. This was used in the next step without further purification.

5 (d) 6(R)-[2-[8(S)-(2,2-Dimethyl-3-methoxy-
3-oxopropionyloxy)-2(S),6(R)-dimethyl-
1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-
ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-
2H-pyran-2-one

To a stirred solution of the compound (1c) (3.8 g, 6.75 mmol) in tetrahydrofuran (25 ml) was added acetic acid (1.2 g, 20 mmol) and tetra-n-butylammonium fluoride.3H₂O (4.73 g, 15 mmol). The reaction mixture was heated to 60-70°C for 4 hours.

The reaction mixture was then cooled to ambient temperature and poured into diethyl ether (200 ml). The mixture was washed with 1N hydrochloric acid (10 ml), saturated aqueous sodium bicarbonate (10 ml) and saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to a viscous oil. The oil was chromatographed on a 5 x 18 cm column of silica gel eluted with 15 percent acetone:methylene chloride to afford the product as a solid m.p. 94-7°C. This material was rechromatographed on a 5 x 17 cm column of silica gel eluted with 20 percent isopropanol/hexane (1L) and 25 percent isopropanol/hexane to give the desired product, which after trituration in hexane was a white solid m.p. 103-4°C

30 Anal. Calc'd. for $C_{25}H_{36}O_7$
C, 66.94; H, 8.09
Found C, 67.10; H, 8.37

NMR (CDCl₃) δ =0.88 (3H, d, J=7Hz), 1.06 (3H, d, J=7Hz), 1.42 (6H, s), 3.66 (3H, s), 4.38 (H, m), 4.55 (H, m), 5.42 (H, m), 5.49 (H, m), 5.78 (H, dd, J=10Hz, 6Hz), 5.96 (H, d, J=10Hz)

5

EXAMPLE 2

Preparation of 6(R)-[2-[8(S)-(2,2-Dimethyl-3-methoxycarbonylpropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a-(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

10

(a) 4-Methyl 2,2-dimethylsuccinate (2a)

To a stirred solution of 2,2-dimethylsuccinic acid (25 g, 171 mmol) in methanol (125 ml) was added concentrated sulfuric acid (1 ml) and the reaction mixture was refluxed for 2 hours. The majority of the methanol was removed in vacuo and the residue treated with saturated aqueous sodium bicarbonate (100 ml). The mixture was extracted with diethyl ether (200 ml). The aqueous phase was acidified with 12N hydrochloric acid and then saturated with sodium chloride. This mixture was extracted with diethyl ether (3 x 100 ml). The combined extracts were washed with saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to give a colorless oil. The oil was distilled at reduced pressure to yield the desired product. b.p. 112-115°C at 0.3 mmHg.

20

25

NMR(CDCl₃) δ =1.31 (6H, s), 2.62 (2H, s), 3.65 (3H, s).

30

(b) 4-Methyl 2,2-dimethylsuccinyl chloride
(2b)

To a stirred solution of the compound
(2a)(4.8 g, 30 mmol) in benzene (20 ml) and oxalyl
5 chloride (4.18 g, 33 mmol) was added dimethylformamide
(1 drop) and the reaction mixture stirred for 1 hour
at ambient temperature. To the reaction mixture was
added dimethylformamide (1 drop) and the reaction
mixture stirred for an additional 1 hour at ambient
10 temperature. The solvent was removed in vacuo and
the residue, distilled at reduced pressure to yield
the desired product as a pale yellow liquid. b.p.
96-98°C at 17 mmHg.

NMR(CDCl₃) δ=1.39 (6H, s), 2.74 (2H, s),
15 3.70 (3H, s).

(c) 6(R)-[2-[8(S)-(2,2-Dimethyl-3-methoxy-
carbonylpropionyloxy)-2(S),6(R)-dimethyl-
1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-
20 ethyl]-4(R)-(dimethyl-tert-butylsilyl-
oxy)-3,4,5,6-tetrahydro-2H-pyran-2-one
(2c)

Utilizing the general procedure of Example
1(c), 6(R)-[2-[8(S)-hydroxy-2(S),6(R)-dimethyl-
25 1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-
(tert-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2H-
pyran-2-one (1.08 g, 2.5 mmol) was reacted with the
compound (2b) (0.89 g, 5.0 mmol) to give the desired
product as a viscous pale yellow oil.

(d) 6(R)-[2-[8(S)-(2,2-Dimethyl-3-methoxy-carbonylpropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-ethyl]-4(R)-hydroxy-3,4,5,6-tetra-
5 hydro-2H-pyran-2-one

Utilizing the general procedure of Example 1(d), the compound (2c) (1.4 g, 2.42 mmol) was converted into the desired product.

Anal. Calc'd for $C_{26}H_{38}O_7$:

10 C, 67.51; H, 8.28.

Found C, 67.41; H 8.66.

NMR ($CDCl_3$) δ =0.91 (3H, d, J=7Hz), 1.11 (3H, d, J=7Hz), 1.28 (3H, s), 1.30 (3H, s), 3.65 (3H, s), 4.38 (H, m), 4.70 (H, m), 5.43 (H, m), 5.53 (H, m), 5.38 (H, dd, J=10Hz, 6Hz), 6.00 (H, d, J=10Hz)
15

EXAMPLES 3-10

Utilizing the general procedures of Example 1 the following compounds are prepared from the
20 appropriately substituted acid or acid chloride and compactin, mevinolin and the dihydro and tetrahydro analogs thereof.

25

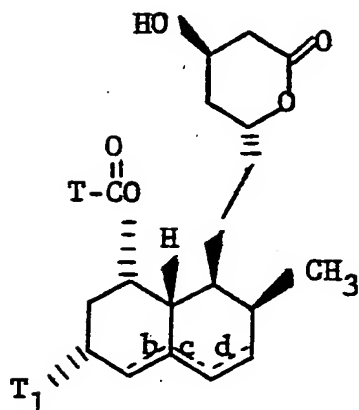
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TABLE 2

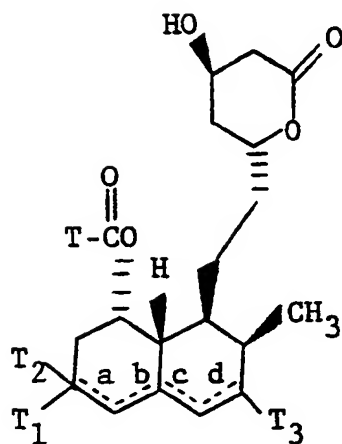
<u>Compound</u>	<u>T</u>	<u>T₁</u>	<u>b</u>	<u>c</u>	<u>d</u>
15					
3	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HOCH}_2 - \text{C} - \text{CH}_3 \\ \\ \text{H} \end{array}$	CH ₃	db	-	db
20					
4	$\begin{array}{c} \text{O} \quad \text{C}_2\text{H}_5 \\ \parallel \quad \\ \text{C}_2\text{H}_5\text{OC} - \text{C} - \text{CH}_3 \end{array}$	CH ₃	db	-	db
25					
5	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \parallel \quad \\ \text{C}_3\text{H}_7\text{OCCH}_2 - \text{C} - \text{CH}_3 \end{array}$	H	-	db	-
30					
6	$\begin{array}{c} \text{OCH}_3 \quad \text{CH}_3 \\ \parallel \quad \\ \text{CH}_3\text{OCC} - \text{C} - \text{CH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	H	-	-	-

db = double bond

TABLE 3

5

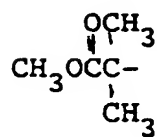
10



15

CompoundTT₁T₂T₃abcd

7



OH

H

H

-

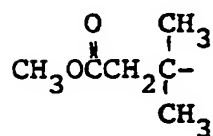
db

-

db

20

8



OH

H

H

-

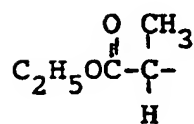
db

-

db

25

9



-

CH₃

OH

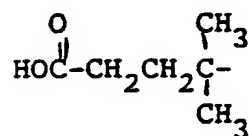
db

-

db

-

10



OH

CH₃

H

-

-

-

-

30

EXAMPLE 11

Preparation of 6(R)-[2-[8(S)-[3-(Diethylamino)-2,2-dimethyl-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,-
6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
5 3,4,5,6-tetrahydro-2H-pyran-2-one

(a) Methyl 2,2-dimethylmalonate (11a)

To a stirred solution of dimethyl 2,2-dimethylmalonate (22.1 g, 138 mmol) in methanol (40 ml) at ambient temperature was added dropwise a
10 solution sodium hydroxide (5.52 g, 138 mmol) in water (20 ml). The reaction mixture was stirred for about 16 hours and then concentrated in vacuo at ambient temperature. The aqueous residue was cooled to 0-5°C and acidified with 6N hydrochloric acid. The aqueous
15 mixture was saturated with sodium chloride and extracted with diethyl ether (2 x 150 ml). The combined extracts were washed with saturated aqueous sodium chloride (2 x 100 ml), dried over magnesium sulfate and concentrated in vacuo to give a colorless
20 oil. The oil was purified by distillation at 15 mmHg to give the desired product which solidified on cooling. mp 35-8°C.

NMR(CDCl₃) δ=1.50 (6H, s), 3.78 (3H, s).

25 (b) Methyl 2,2-dimethylmalonyl chloride (11b)

To a stirred solution of the compound (11a) (5.0 g, 34.2 mmol) in dry benzene (25 ml) and dimethylformamide (2 drops) at ambient temperature was added oxalyl chloride (3.73 ml, 42.8 mmol). The
30 reaction mixture was stirred for about 2 hours and

the solvent removed in vacuo. The desired product was distilled at reduce pressure to yield a colorless liquid. bp 61-2°C at 15 mmHg.

NMR(CDCl₃) δ =1.56 (6H, s), 3.80 (3H, s).

5

(c) Methyl 3-(diethylamino)-2,2-dimethyl-3-
oxopropionate (11c)

To a stirred solution of freshly distilled compound (11b) (6.5 g, 39.5 mmol) in diethyl ether
10 (100 ml) was added dropwise at ambient temperature a solution of freshly distilled diethylamine (6.35 g, 8.69 mmol) in diethyl ether (50 ml). The reaction mixture was stirred for 2 hours at ambient temperature and the diethylamine hydrochloride precipitate was
15 removed by filtration. The filtrate was concentrated in vacuo to give a pale yellow oil. The oil was distilled at reduced pressure to give the desired product as a colorless liquid. bp 80-82°C at 0.3 mmHg.

20 NMR(CDCl₃) δ =1.11 (6H, t, J=7Hz), 1.43 (6H, s), 3.14 (2H, m), 3.37 (2H, m), 3.73 (3H, s).

(d) 3-(Diethylamino)-2,2-dimethyl-3-oxopropionic acid
(11d)

25 A stirred suspension of the compound (11c) (7.6 g, 37.8 mmol) in 1N sodium hydroxide (50 ml, 50 mmol) was heated at 70°C for 5 hours and then cooled to 0-5°C. The reaction mixture was acidified with concentrated hydrochloric acid (5 ml, 60 mmol) and a
30 colorless solid crystallized. The solid was dissolved in diethyl ether and organic phase dried over

magnesium sulfate and concentrated in vacuo to give a colorless solid. The solid was recrystallized from diethyl ether/hexane to yield the desired product as colorless crystals. mp 110-112°C

- 5 Anal. Calc'd. for $C_9H_{17}NO_3$.
 C, 57.73; H, 9.15; N, 7.48.
Found: C, 58.09; H, 9.46; N, 7.19

10 (e) 3-(Diethylamino)-2,2-dimethyl-3-oxopropionyl
chloride (11e)

- To a stirred suspension of the compound (11d) (6.6g, 35.2 mmol) in benzene (25 ml) and freshly distilled oxalyl chloride (5.6g, 44 mmol) was added at ambient temperature dimethylformamide (2
15 drops). After 1 hour at ambient temperature, additional dimethylformamide (2 drops) was added and the reaction mixture stirred for additional hour. The solvent was removed in vacuo to give a yellow liquid. The liquid was distilled at reduced pressure
20 to give the desired product as a colorless liquid bp 74-5°C at 0.3 mm Hg.

 NMR($CDCl_3$) δ =1.17 (6H, t, J=7Hz), 1.55 (6H,s), 3.30 (4H, m).

25 (f) 6(R)-[2-[8(S)-[3-(Diethylamino)-2,2-dimethyl-3-oxopropionyloxy]2(S),6(R)-dimethyl-1,2,6,7,-8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (11f)

- 30 To a stirred solution of 6(R)-[2-[8(S)-hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)] ethyl]-4(R)-(tert-butyldimethylsilyl-

oxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (1.08 g, 2.5 mmol) in dry pyridine (10 ml) containing 4-pyrrolidinopyridine (148 mg, 1 mmol) was added at 100°C the compound (11e) (1.03 g, 5.0 mmol). After 3 hours additional compound (1e) (0.5 g) and 4-pyrrolidinylpyridine (148 mg) were added. After 8 hours additional compound (11e) (0.5 g) was added and reaction mixture heated at 100°C for a total of 12 hours. The solvent was removed in vacuo and the residue partitioned between diethyl ether (200 ml) and water (25 ml) containing 6N hydrochloric acid (5 ml). The organic phase was washed with saturated aqueous sodium chloride (25 ml), saturated aqueous sodium bicarbonate (20 ml) and saturated aqueous sodium chloride (25 ml), dried over magnesium sulfate and concentrated in vacuo to give a reddish orange oil. The oil was chromatographed on a 3 x 15 cm column of silica gel eluted with 50 percent diethyl ether/hexane to afford the desired product as a viscous yellow oil.

NMR(CDCl₃) δ=0.01(3H, s), 0.08(3H, s), 0.87(3H, d, J=7Hz), 0.89(9H, s), 1.03(3H, d, J=7Hz), 1.40(6H, s), 3.22(4H, m) 4.32(H, m), 4.64(H, m), 5.48(H, m), 5.60(H, m), 5.76(H, dd, J=10Hz, 6Hz), 5.96(H, d, J=10Hz).

(g) 6(R)-[2-[8(S)-[3-(Diethylamino)-2,2-dimethyl-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a-(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

To a stirred solution of the compound (11f) (1.5g, 2.5 mmol) in tetrahydrofuran (20 ml) was added acetic acid (573 ml, 10 mmol) and tetra-n-butyl-ammonium fluoride (7.5 ml, 1M in tetrahydrofuran, 7.5 mmol). The reaction mixture was heated at 70°C for 3 hours. The reaction mixture was then cooled to ambient temperature and poured into diethyl ether (200 ml). The mixture was washed with water (25 ml) containing 6N hydrochloric acid (3 ml), saturated aqueous sodium chloride (25 ml), saturated aqueous sodium bicarbonate (2 x 25 ml) and saturated aqueous sodium chloride (25 ml), dried over magnesium sulfate and concentrated in vacuo to give a pale yellow oil. The oil was chromatographed on a 3 x 15 cm column of silica gel eluted with 25 percent acetone:methylene chloride (500 ml) and 30 percent acetone:methylene chloride to give the product as a colorless solid. mp 138-140°C.

Anal. Calc'd. for $C_{28}H_{43}NO_6$:

C, 68.68; H, 8.85; N, 2.86.

Found: C, 68.70; H, 8.93; N, 2.78

NMR($CDCl_3$) δ =0.89 (3H, d, J=7Hz), 1.09(3H, d, J=7Hz), 1.12(6H, m), 1.39(3H, s), 1.42 (3H, s), 3.18(4H, m), 4.38(H, m), 4.60(H, m), 5.49(H, m), 5.57(H, m), 5.68(H, dd, J=10Hz, 7Hz), 5.98(H, d, J=10Hz).

EXAMPLE 12

Preparation of 6(R)-[2-[8(S)-(2,2-Dimethyl-3-morpholino-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

(a) Methyl 2,2-dimethyl-3-morpholino-3-oxopropionate
(12a)

Utilizing the general procedure of Example 11(c), the compound (11b) (5.76g, 35 mmol) was reacted with freshly distilled morpholine (6.1 g, 70 mmol) to obtain the desired product as solid. mp 69-71°C.

Anal. Calc'd. for $C_{10}H_{17}NO_4$

C, 55.80; H, 7.96; N, 6.51.

Found C, 55.68; H, 8.20; N, 6.66.

(b) 2,2-Dimethyl-3-morpholino-3-oxopropionyl chloride
(12b)

Utilizing the general procedures of Examples 11(d) and 11(e), the compound (12a) (6.9 g, 32 mmol) was converted into the desired product as viscous pale yellow liquid. bp 105-7°C at 0.3 mmHg.

NMR(CDC l_3) δ =1.50 (6H, s), 3.55 (4H, m), 3.71 (4H, m).

(c) 6(R)-[8(S)-(2,2-Dimethyl-3-morpholino-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one
(12c)

Utilizing the general procedure of Example 11(f), 6(R)-[2-[8(S)]-hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-

(tert-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (1.08 g, 2.5 mmol) was reacted with the compound (2b) (1.09 g, 5.0 mmol) to yield the desired product as a colorless foam.

5

(d) 6(R)-[2[8(S)-(2,2-Dimethyl-3-morpholino-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

10

Utilizing the general procedure of Example 11(g), the compound (12c) (0.9 g, 1.46 mmol) was converted into the desired product as a colorless solid. mp 176-9°C.

Anal. Calc,d. for $C_{28}H_{41}NO_7$.

15

C, 66.77; H, 8.21; N, 2.78.

Found: C, 67.01; H, 8.23; N, 3.00.

NMR($CDCl_3$) δ =0.88(3H, d, J=7Hz), 1.06(3H, d, J=7Hz), 1.41(3H, s), 1.44(3H, s), 3.41(4H, m), 3.65(4H, m), 4.38(H, m), 4.62(H, m) 5.49(H, m), 5.58(H, m), 5.80(H, dd, J=10Hz, 6Hz), 5.97(H, d, J=10Hz).

20

EXAMPLE 13

25 Preparation of 6(R)-[2-[8(S)-[3-(Dimethylamino)-2,2-dimethyl-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

Utilizing the general procedures of Example 11, the desired product was prepared from 6(R)-[2-[8(S)-hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-(tert-butyldimethyl-

30

silyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (1.08 g, 2.5 mmol) and 3-(dimethylamino)-2,2-dimethyl-3-oxopropionyl chloride (0.888 g, 5.0 mmol) which was prepared from dimethylamine and the compound 11(b).

5 The desired product was a colorless solid. mp 95-97°C.

Anal. Calc'd. for $C_{26}H_{39}NO_6$:

C, 67.65; H, 8.52; N, 3.04.

Found: C, 67.53; H, 8.77; N, 3.13.

NMR($CDCl_3$) δ =0.90(3H, d, J=7Hz), 1.06(3H, d, J=7Hz), 1.44(6H, s), 2.94(6H, s), 4.41(H, m), 4.64(H, m), 5.48(H, m), 5.64(H, m), 5.80 H, dd, J=10Hz, 6Hz) 5.99(H, d, J= 10Hz).

EXAMPLE 14

15 Preparation of 6(R)-[2-[8(S)-[4-(Dimethylamino)-2,2-dimethyl-4-oxobutanoyloxy]-2(S),6(R)-dimethyl-1,2,6,-7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

(a) 4-(Dimethylamino)-2,2-dimethyl-4-oxobutanoic acid
20 (14a)

To a stirred solution of dimethylamine (6.8 g, 150 mmol) in tetrahydrofuran (150 ml) at 0°C was added dropwise a solution of 2,2-dimethylsuccinic anhydride (4.8 g, 37.5 mmol) in tetrahydrofuran (50 ml) and reaction mixture stirred for about 16 hours at ambient temperature. The solvent was removed in vacuo and the residue was washed with 6N hydrochloric acid (5 ml) and methylene chloride was added to dissolve the precipitate. The solution was washed with saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated to a pale

yellow solid. The solid was dissolved in methylene chloride (20 ml) and the desired product precipitated upon the addition of hexane to yield a colorless solid. mp 119-121°C.

5 NMR(CDCl₃) δ=1.33 (6H, s), 2.64 (2H, s),
3.02 (3H, s), 3.07 (3H, s).

(b) 6(R)-[2-[8(S)-[4-(Dimethylamino)-2,2-dimethyl-4-oxobutanoyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a-hexahydronaphthyl-1(S)]ethyl]-4(R)-(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one
10 (14b)

To a stirred solution of the compound (14a) (0.866 g, 5 mmol) and N-methylmorpholine (550 ml, 5 mmol) in methylene chloride (10 ml) at -5°C was added dropwise a solution of 2,4-dichloro-6-methoxy-triazine (0.9 g, 5 mmol) in methylene chloride (10 ml). The reaction mixture was stirred for 2 hours under nitrogen at 0 to -10°C. To the reaction mixture was then added dropwise 6(R)-[2-[8(S)-hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)-ethyl-4(R)-(tert-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (108 g, 2.5 mmol) in methylene chloride (10 ml) and the reaction mixture was heated to reflux. After 4 hours, a solution of the compound (4a) (0.433 g, 2.5 mmol) and 2,4-dichloro-6-methoxy-triazine (0.45 g, 2.5 mmol) in methylene chloride (20 ml) was added. After another hour at reflux, additional compound (4a) (0.433 g, 2.5 mmol) and 2,4-dichloro-6-methoxytriazine (0.45 g, 2.5 mmol) was added and the reaction mixture refluxed for

about 16 hours. The reaction mixture was cooled and poured into diethyl ether (200 ml). The mixture was washed with water (2 x 25 ml), 1N hydrochloric acid (10 ml), saturated aqueous sodium chloride (25 ml),
5 saturated aqueous sodium bicarbonate (25 ml) and saturated aqueous sodium chloride (25 ml), dried over magnesium sulfate and concentrated in vacuo to give a viscous oil. The oil was chromatographed on a 5 x 15 cm column of silica gel eluted with 5 percent acetone/
10 methylene chloride to yield the desired product as a colorless foam.

NMR CDCl₃) δ =0.08(6H, s), 0.89(9H, s), 0.89(3H, d, J=7Hz), 1.10(3H, d, J=7Hz), 1.26(3H, s), 1.29(3H, s), 2.86(3H, s), 2.96(3H, s) 4.28(H, m),
15 4.57(H, m), 5.45(H, m) 5.49(H, m), 5.80(H, dd, J=10Hz, 6Hz), 5.98(H, d, J=10Hz).

(c) 6(R)-[2-[8(S)-[4-(Dimethylamino)-2,2-dimethyl-4-oxobutanoyl]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
20 hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,-
5,6-tetrahydro-2H-pyran-2-one

Utilizing the general procedure of Example 11(g), the compound (14b) (1.6 g, 2.5 mmol) was converted into the desired product as an amorphorous
25 solid.

Anal. Calc'd. for C₂₇H₄₁NO₆.1/2H₂O:

C, 66.91; H, 8.74; N, 2.89.

Found: C, 67.30; H, 9.11; N, 3.03.

NMR(CDCl₃) δ =0.90(3H, d, J=7Hz), 1.11(3H, d, J=7Hz), 1.30(3H, s), 1.34(3H, s), 2.88(3H, s),
30 3.01(3H, s), 4.33(H, m), 4.62(H, m), 5.39(H, m), 5.51(H, m), 5.82(H, dd, J=10Hz, 6Hz), 6.00(H, d, J=10Hz).

EXAMPLE 15

Preparation of 6(R)-[2-[8(S)-[2,2-dimethyl-3-(methyl-
amino)-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,-
7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
5 3,4,5,6-tetrahydro-2H-pyran-2-one

Utilizing the general procedures of Example
11(a) through 11(d) and Example 14(b) and 14(c), the
desired product was prepared from 6(R)-[2-[8(S)-
hydroxy-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-
10 naphthyl-1(S)]ethyl]-4(R)-(tert-butyldimethylsilyl-
oxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (1.08 g, 2.5
mmol) and 2,2-dimethyl-3-(methylamino)-3-oxopropionic
acid (0.726 g, 5 mmol) which was prepared from
methylamine and the compound 11(b). The desired
15 product was a colorless solid. mp 171-73°C.

Anal. Calc'd. for $C_{25}H_{37}NO_6$:

C, 67.09; H, 8.33; N, 3.13.

Found: C, 66.88; H, 8.39; N, 3.39.

NMR($CDCl_3$) δ =0.89(3H, d, J=7Hz), 1.06(3H,
20 d, J=7Hz), 1.43(3H, s), 1.45(3H, s), 2.89(3H, d,
J=5Hz) 4.36(H, m), 4.63(H, m), 5.37(H, m), 5.52(H, m),
5.80(H, dd, J=10Hz, 6Hz), 5.99(H, d, J=10Hz).

EXAMPLE 16-25

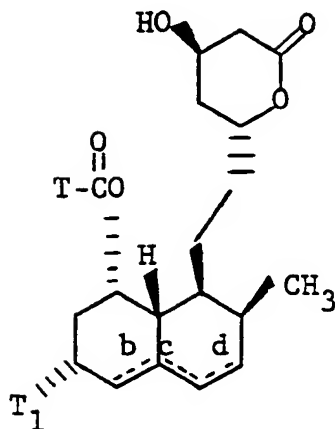
25 Utilizing the general procedures of Example
11 the following compounds are prepared from the
appropriately substituted acid chloride and compactin
mevinolin and the dihydro and tetrahydro analogs
thereof.

30

TABLE 4

5

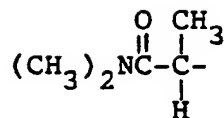
10



15

CompoundTT₁bcd

16

CH₃

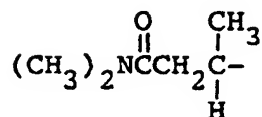
db

-

db

20

17

CH₃

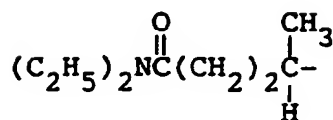
-

-

-

25

18



H

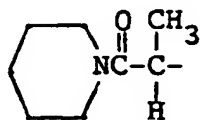
-

db

-

30

19



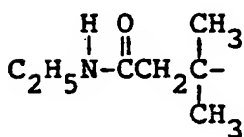
H

-

-

-

20

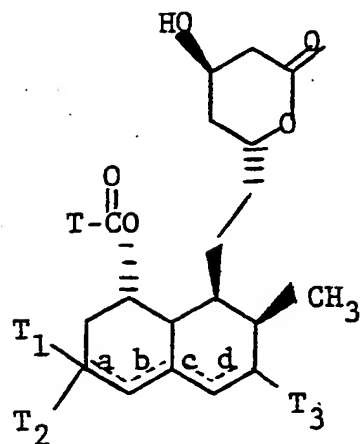
CH₃

-

db

-

TABLE 5



Compound	T	T ₁	T ₂	T ₃	a	b	c	d
21	$\begin{array}{c} \text{OCH}_3 \\ \\ (\text{CH}_3)_2\text{NCC}- \\ \\ \text{CH}_3 \end{array}$	OH	H	H	-	db	-	db
22	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \quad \\ (\text{CH}_3)_2\text{NCCCH}_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	OH	H	H	-	-	-	-
23	$\begin{array}{c} \text{OCH}_3 \\ \\ (\text{C}_2\text{H}_5)_2\text{NCC}- \\ \\ \text{CH}_3 \end{array}$	H	-	OH	db	-	db	-
24	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \quad \\ (\text{C}_2\text{H}_5)_2\text{NCCCH}_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	CH ₃	-	OH	db	-	db	-
25	$\begin{array}{c} \text{HOCH}_3 \\ \\ \text{CH}_3\text{NCC}- \\ \\ \text{CH}_3 \end{array}$	OH	CH ₃	H	-	db	-	db

EXAMPLE 26

Preparation of 6(R)-[2-[8(S)-[2-Methyl-2-(methylthio)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexa-
hydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetra-
5 hydro-2H-pyran-2-one

(a) Ethyl 2-methyl-2-(methylthio)-propionate (26a)

To a stirred solution of sodium hydroxide
(16 g, 0.4 mol) in water (100 ml) saturated with
10 methyl mercaptan (20 g, 0.416 mol) at 15°C was added
dropwise ethyl 2-bromo-2-methylpropionate (19.5 g,
0.1 mol). The reaction mixture was stirred at ambient
temperature for 2 days. The reaction mixture was
cooled to about 0°C and acidified with concentrated
15 hydrochloric acid (34 ml). The mixture was extracted
with diethyl ether (3 x 100 ml). The combined
extracts were washed with saturated aqueous sodium
chloride, dried over magnesium sulfate and
concentrated in vacuo to give a yellow liquid. The
20 liquid was distilled at reduced pressure to yield the
desired product as a colorless liquid, b.p. 84-85°C
at 15 mm Hg.

Anal. Calc'd. for $C_7H_{14}O_2S$:

C, 51.82; H, 8.70.

25 Found: C, 51.03; H, 8.66.

NMR($CDCl_3$) δ =1.29 (3H, t, J=7Hz), 1.51
(6H, s), 2.12 (3H, s), 4.19 (2H, d, J=7Hz).

(b) 2-Methyl-2-(methylthio)-propionic acid (26b)

30 To a stirred solution of the compound (26a)
(14.6 g, 90 mmol) in methanol (25 ml) was added
dropwise a solution of sodium hydroxide (4.0 g, 0.1

mol) in water (10 ml) and the reaction mixture stirred at ambient temperature for about 16 hours. The solvent was removed in vacuo. The aqueous phase was cooled to about 0°C and acidified with concentrated hydrochloric acid (9 ml). The mixture was extracted with diethyl ether (3 x 75 ml). The combined extracts were washed with saturated aqueous sodium chloride (2 x 50 ml), dried over magnesium sulfate and concentrated in vacuo to a pale yellow liquid. The liquid was distilled at reduced pressure to give a colorless liquid which solidified on standing, b.p. 119-121°C at 15 mm Hg.

NMR(CDCl₃) δ=1.53 (6H, s), 2.17 (3H, s).

15 (c) 2-Methyl-2-(methylthio)-propionyl chloride (26c)

To a stirred solution of the compound (26b) (5.37 g, 40 mmol) and oxalylchloride (5.58 g, 44 mmol) in benzene (25 ml) was added dimethylformamide (2 drops). After 2 hours, the solvent was removed in vacuo to give a yellow liquid. The liquid was distilled at reduced pressure to give the desired product as a colorless liquid, b.p. 64-5°C at 15 mm Hg.

NMR(CDCl₃) δ=1.59 (6H, s), 2.09 (3H, s).

25

(d) 6(R)-[2-[8(S)-[2-Methyl-2-(methylthio)propionyl-oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a-(R)-hexahydro-naphthyl-1(S)]ethyl]-4(R)-(dimethyl-tert-butyl-silyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (26d)

30

A solution of 6(R)-[2-[8(S)-hydroxy-2(S),-6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-

- 1(S)]ethyl]-4(R)-(tert-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (1.8 g, 2.5 mmol) in dry pyridine (10 ml) containing 4-pyrrolidinopyridine (148 mg, 1 mmol) was heated to 100°C under nitrogen.
- 5 To the reaction mixture was added the compound (26c) (0.763 g, 5 mmol). After 5 hours additional compound (1c) (0.763 g, 5 mmol) was added and the reaction mixture stirred for a total of 11 hours. The reaction mixture was cooled and poured into diethyl
- 10 ether (200 ml). The mixture was washed with 6N hydrochloric acid (2 x 10 ml), saturated aqueous sodium chloride (20 ml), saturated aqueous sodium bicarbonate (10 ml) and saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate
- 15 and concentrated in vacuo to afford a viscous brown oil. The oil was chromatographed on 17 x 40 cm column of silica gel eluted with 50 percent diethyl ether/hexane to yield the desired product as a pale yellow foam.
- 20 NMR(CDCl₃) δ=0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.46 (6H, s), 2.10 (3H, s), 4.30 (H, m), 4.61 (H, m), 5.33 (H, m), 5.53 (H, m), 5.78 (H, dd, J=10Hz, 6Hz), 5.98 (H, d, J=10Hz).
- 25 (e) 6(R)-[2-[8(S)-[2-methyl-2-(methylthio)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,-7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one
- To a stirred solution of the compound (26d)
- 30 (110 mg, 0.2 mmol) in tetrahydrofuran (5 ml) were added acetic acid (48 mg, 0.8 mmol) and tetra-n-butyl-ammonium fluoride • 3H₂O (189 mg, 0.6 mmol). The

reaction mixture was heated at 65-70°C for 3 hours and then cooled. The reaction mixture was poured into diethyl ether (200 ml). The mixture was washed with 1N hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml) and saturated aqueous sodium chloride (2 x 10 ml), dried over magnesium sulfate and concentrated in vacuo to give a viscous yellow oil. The oil was chromatographed on a 3 x 15 cm column of silica gel eluted with 10 percent acetone/methylene chloride (500 ml) and 20 percent acetone/methylene chloride to afford the desired product which after recrystallization from diethyl ether/hexane was a colorless solid, m.p. 108-9°C.

Anal. Calc'd. for $C_{24}H_{36}O_5S$:

15 C, 66.02; H, 8.31.

Found: C, 65.91; H, 8.31.

NMR($CDCl_3$) δ 0.89(3H, d, J=7Hz),
1.10(3H, d, J=7Hz), 1.46(6H, s) 2.11(3H, s), 4.40(H, m),
4.51(H, m) 5.34(H, m) 5.51(H, m), 5.78(H, dd, J=10Hz,
20 6Hz), 5.98(H, d, J=10Hz)

EXAMPLE 27

Preparation of 6(R)-[2-[8(S)-[2-Methyl-2-(methylsulfinyl)propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,-
25 8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,-
4,5,6-tetrahydro-2H-pyran-2-one

(a) 6(R)-[2-[8(S)-[2-Methyl-2-(methylsulfinyl)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-(dimethyl-tert-
30 butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one

To a stirred solution of the compound (26d)
(260 mg, 0.47 mmol) in methylene chloride at -78°C

was added dropwise 3-chloroperbenzoic acid (85.5 mg, 0.49 mmol) in methylene chloride (2 ml). The reaction was stirred for 1 hour at -78°C and additional 3-chloroperbenzoic acid (17 mg) in methylene chloride (1 ml) was added. After an additional hour at -78°C, dimethylsulfide (100 ml) was added and the mixture warmed to ambient temperature. The mixture was poured into diethyl ether (150 ml). The mixture was washed with saturated aqueous sodium bicarbonate (20 ml) and saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to give the product as a pale yellow foam. This product was used in the next step without further purification.

15

(b) 6(R)-[2-[8(S)-[2-methyl-2-(methylsulfinyl)-propionyloxy]-2(S),6(R)-dimethyl- 1,2,6,7,8,-8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one

20

Utilizing the general procedure of Example 26(e), the compound (27a) (270 mg, 0.47 mmol) was converted into the desired product as a mixture of diastereomers, m.p. 113-116°C.

Anal. Calc'd. for $C_{24}H_{36}O_6S \cdot 1/2H_2O$:

25

C, 62.44; H, 8.06.

Found: C, 62.57; H, 7.95.

NMR(CDCl₃) δ =0.89(3H, d, J=7Hz),

1.08(3H, m), 1.42-1.51(6H, m) 2.50(1.5 H,s), 2.56

(1.5 H, s), 4.30(H, m) 4.64(H, m) 5.44(H, m), 5.52(H,

30 m), 5.82 (H, dd, J=10HZ, 6Hz), 6.0 (H, d, J= 10Hz).

EXAMPLE 28

Preparation of 6(R)-[2-[8(S)-[2-Methyl-2-(methyl-
sulfonyl)propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,-
8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
5 3,4,5,6-tetrahydro-2H-pyran-2-one

(a) 2-Methyl-2-(methanolsulfonyl)-propionic acid (28a)

To a stirred solution of the compound (26b)
(5.9 g, 44 mmol) in ethyl acetate (50 ml) at 0°C was
10 added portionwise 3-chloroperbenzoic acid (16.7 g, 96
mmol). The reaction mixture was warmed to ambient
temperature and stirred for 3 hours. The reaction
mixture was heated at 60°C for 30 minutes and cooled
to ambient temperature. The resultant precipitate
15 was removed by filtration and filtrate concentrated
to dryness to give a solid which was suspended in
methylene chloride (100 ml). The suspension was
cooled to 0-5°C and filtered. The filtrate was
concentrated to dryness to afford a solid. The solid
20 was recrystallized from ethyl acetate/hexane to give
the desired product as a colorless solid, m.p.
153-155°C.

NMR(CDCl₃) δ=1.70 (6H, s), 3.12 (3H, s).

25

30

(b) 6(R)-[2-[8(S)-[2-Methyl-2-(methylsulfinyl)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
3,4,5,6-tetrahydro-2H-pyran-2-one

5 Utilizing the general procedures of Example
26(c) through 26(e), the compound (28a) (2.5 g, 14.8
mmol) was converted into the desired product as a
colorless solid, m.p. 149-151°C.

Anal. Calc'd. for $C_{24}H_{36}O_7S$:

10 C, 61.51; H, 7.74.

Found: C, 61.38; H, 8.03.

NMR($CDCl_3$) δ =0.89(3H, d, J=7Hz), 1.06
3H,d,J=7Hz), 1.60(3H, s), 1.64 (3H, s), 3.11 (3H, s)
15 4.35(H, m) 4.64(H, m), 5.74(H, m), 5.52(H, m),
5.82(H, dd, J=10Hz, 6Hz), 5.98 (H, d, J=10 Hz).

EXAMPLES 29-37

Utilizing the general procedures of Example
20 26 the following compounds are prepared from the
appropriately substituted acid chloride and compactin
mevinolin and the dihydro and tetrahydro analogs
thereof.

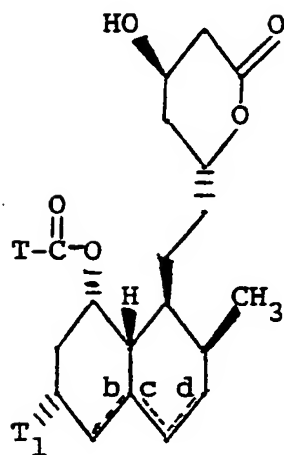
25

30

TABLE 6

5

10



15

Compound	T	T ₁	b	c	d
29	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{SCH}_2\text{C}- \\ \\ \text{H} \end{array}$	CH ₃	db	-	db
30	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \quad \\ \text{C}_2\text{H}_5\text{SCH}_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	CH ₃	-	db	-
31	$\begin{array}{c} \text{O} \quad \text{CH}_3 \\ \quad \\ \text{n-C}_3\text{H}_7\text{SCH}_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	H	db	-	db

30

2212S/0985A

- 51 -

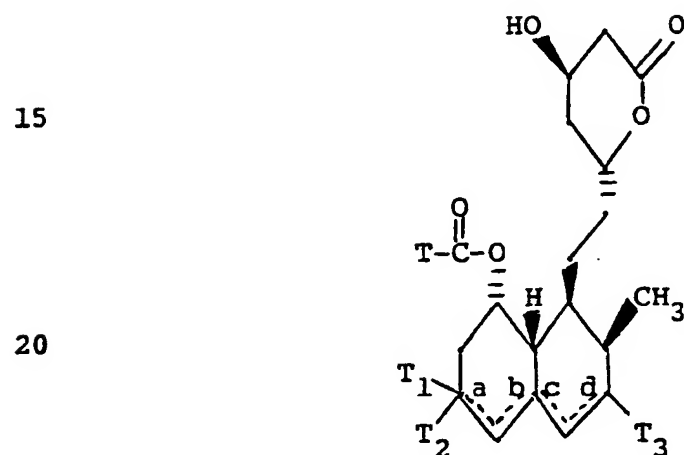
17377Y

Compound	T	T ₁	b	c	d
----------	---	----------------	---	---	---

5 32	$\text{CH}_3\text{S}(\text{CH}_2)_2\overset{\text{CH}_3}{\underset{\text{H}}{\text{C}}}-$	CH ₃	-	-	-
------	---	-----------------	---	---	---

10 33	$\text{C}_2\text{H}_5\overset{\text{O}_2}{\text{S}}(\text{CH}_2)_2\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}-$	H	-	db	-
-------	---	---	---	----	---

TABLE 7



Compound	T	T ₁	T ₂	T ₃	a	b	c	d
----------	---	----------------	----------------	----------------	---	---	---	---

25 34	$\text{CH}_3\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{SC}}}-$	OH	H	H	-	db	-	db
-------	--	----	---	---	---	----	---	----

30 35	$\text{C}_2\text{H}_5\overset{\text{O}}{\text{SCH}_2}\overset{\text{CH}_3}{\underset{\text{H}}{\text{C}}}-$	OH	CH ₃	H	-	db	-	db
-------	---	----	-----------------	---	---	----	---	----

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- 52 -

17377Y

Compound	T	<u>T</u> ₁	<u>T</u> ₂	<u>T</u> ₃	<u>a</u>	<u>b</u>	<u>c</u>	<u>d</u>
5 36	$\begin{array}{c} \text{O}_2 \\ \\ \text{C}_3\text{H}_7\text{S}(\text{CH}_2)_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	-	CH ₃	OH	db	-	db	-
10 37	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{SC}- \\ \\ \text{CH}_3 \end{array}$	OH	H	H	-	-	-	-

15

20

25

 db = double bond

30

EXAMPLE 38

Preparation of 6(R)-[2-[8(S)-[2-Methyl-2-(phenylthio)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexa-
hydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetra-
5 hydro-2H-pyran-2-one

(a) 2-Methyl-2-(phenylthio)-propionic acid (38a)

A stirred mixture of thiophenol (11.0 g, 100
mmol), sodium hydroxide (18.0 g, 450 mmol) and
chloroform (14.4 g, 120 mmol) in acetone (100 ml) was
10 gently warmed in a 60°C water bath. The reaction
mixture then exothermed to reflux and was heated at
reflux for 3 hours. The acetone was removed in vacuo
and the resultant residue dissolved in water (500 ml).
The solution was washed with diethyl ether (100 ml)
15 and the aqueous phase was acidified with 12N hydro-
chloric acid. The resulting mixture was extracted
with diethyl ether (3 x 100 ml). The extracts were
combined, washed with brine (2 x 50 ml) dried over
anhydrous magnesium sulfate and concentrated in vacuo
20 to give a yellow liquid. The yellow liquid was
distilled at reduced pressure to afford a colorless
liquid which solidified on standing bp 0.2mm =
125-7°C; mp 62-4°C.

NMR(CDCl₃) δ= 1.00 (6H, s), 7.31-7.40
25 (3H, m) 7.52 (2H, m).

(b) 6(R)[2-(8(S)-[2-Methyl-2-(phenylthio)-propionoyl-
oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-
naphthyl-1(S)]ethyl-4(R)-(tert-butyldimethylsilyloxy)-
30 3,4,5,6-tetrahydro-2H-pyran-2-one (38b)

To a stirred solution of the compound (38a)
0.785 g, 4.0 mmol) and N-methylmorpholine (0.44 ml, 4

mmol) in methylene chloride (10 ml) at -5°C was added dropwise a solution of 2,4-dichloro-6-methoxytriazine (0.72 g, 4.0 mmol) in methylene chloride (10 ml). The reaction mixture was stirred for 1 hour under
5 nitrogen at 0°C. To the reaction mixture was then added dropwise 6(R)-[2-[8(S)-hydroxy-2-(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1-(S)ethyl-4(R)-(tert-butyldimethylsilyloxy)-3,4,5,6-tetrahydro-
10 2H-pyran-2-one (87 mg, 2.5 mmol) in methylene chloride (10 ml) and the reaction mixture was heated to reflux. After 24 hours, a solution of the compound (38a) (0.785 g, 0.4 mmol) and 2,4 dichloro-6-methoxytriazine (0.72 g, 4.0 mmol) in methylene
15 chloride (20 ml) was added. After another 48 hours at reflux, the reaction mixture was cooled and poured into diethyl ether (200 ml). The mixture was washed with water (25 ml), 1N hydrochloric acid (10 ml), saturated aqueous sodium chloride (25 ml), water (25 ml), saturated aqueous sodium bicarbonate (25 ml) and
20 saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to give a viscous oil. The oil was chromatographed on a 4 x 15 cm column of silica gel eluted with 50 percent diethyl ether/hexane to yield the desired product as
25 a light yellow liquid.

NMR(CDCl₃) δ= 0.01 (6H, s), 0.81 (9H, s), 0.88 (3H, d, J=7Hz), 1.07 (3H, d, J=7Hz), 1.37 (3H,s), 1.42 (3H, s), 4.18 (H, m), 4 (H, m), 5.34 (H, m), 5.51 (H, m), 5.79 (H, dd, J=6Hz, 10Hz), 5.99
30 (H,d, J=10Hz , 7.30-7.41 (3H, m), 7.47 (2H, m).

(c) 6(R)-[2-[8(S)-[2-Methyl-2(phenylthio)-propionoyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (38c)

5 To a stirred solution of the compound (38b) (640 mg, 1.04 mmol) in tetrahydrofuran (20 ml) were added acetic acid (251 mg, 4.17 mmol) and tetra-n-butylammonium fluoride • 3H₂O (3.13 ml, 1M in THF, 3.13 mmol). The reaction mixture was heated to
10 reflux for 4 hours and then cooled. The THF was removed in vacuo. The reaction mixture was then poured into diethyl ether (150 ml). The mixture was washed with water (25 ml) 1N hydrochloric acid (10 ml), water (25 ml) saturated sodium bicarbonate (25
15 ml) and saturated aqueous sodium chloride (2 x 25 ml), dried over magnesium sulfate and concentrated in vacuo to give a yellow foam. The foam was chromatographed on 3 x 15 cm column of silica gel eluted with 15 percent ISO propanol/hexane,
20 triturated with hexane to afford the desired product which after recrystallization from diethyl ether/hexane was a colorless solid, m.p. 132-4°C.

Anal. Calc'd. for C₂₉H₃₈O₅S:

C, 69.84; H, 7.68.

25 Found: C, 70.05; H, 8.04.

NMR(CDCl₃) δ= 0.90 (3H, d, J=Hz), 1.08 (3H, d, J=7Hz), 1.39 (3H, s), 1.45 (3H, s) 4.25 (H, m), 4.52 (H, m), 5.41 (H, m), 5.53 (H, m), 5.80 (H, dd, J=6Hz, 10Hz), 6.00 (H, d, J=10Hz), 7.30-7.41 (3H, m), 7.49 (2H, m).

30

EXAMPLE 39

Preparation of 6(R)-[2-[8(S)-[2-Methyl-2-phenyl-sulfinyl)propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,-
8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,-
5 4,5,6-tetrahydro-2H-pyran-2-one

To a stirred solution of the compound (38c) (99.7 mg, 0.2 mmol) in methylene chloride (10 ml) at -78°C under nitrogen was added dropwise to a solution of 3-chloroperbenzoic acid (34.5 mg, 0.2 mmol) in
10 methylene chloride (5 ml). After one hour, additional 3-chloroperbenzoic acid (34.5 mg, 0.2 mmol) in methylene chloride (5 ml) was added and the reaction mixture stirred for 30 minutes. Dimethylsulfide (100 ml) was then added and the reaction mixture warmed to
15 ambient temperature. The reaction mixture was poured into diethyl ether (200 ml). The solution washed with saturated aqueous sodium bicarbonate (25 ml), and brine (2 x 25 ml), dried over anhydrous magnesium sulfate and concentrated in vacuo to give a viscous
20 oil. The oil was chromatographed on a 3 x 12.5 cm column of silica gel eluted with 25 percent isopropanol/hexane to the desired product which after recrystallization from diethyl ether/hexane afforded a colorless solid: mp 117-119°C.

25 Anal. Calc'd. for $C_{29}H_{38}O_6S$:

C, 67.67; H, 7.44.

Found: C, 68.01; H, 7.75.

NMR($CDCl_3$) δ = 0.90 (3H, d, J=7Hz), 1.10 (3H, d, J=7Hz), 1.27 (6H, s), 4.30 (H, m), 4.68 (H, m), 5.49 (H, m), 5.53 (H, m), 5.84 (H, m), 6.00 (H, m), 7.49-7.61 (5H, m).

EXAMPLES 40-49

Utilizing the general procedures of Example
38 the following compounds are prepared from the
appropriately substituted acid chloride and compactin
5 mevinolin and the dihydro and tetrahydro analogs
thereof.

10

15

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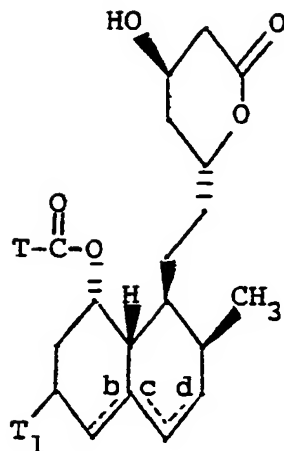
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TABLE 8

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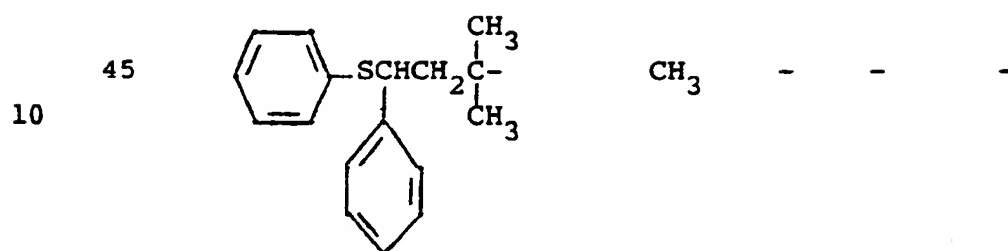
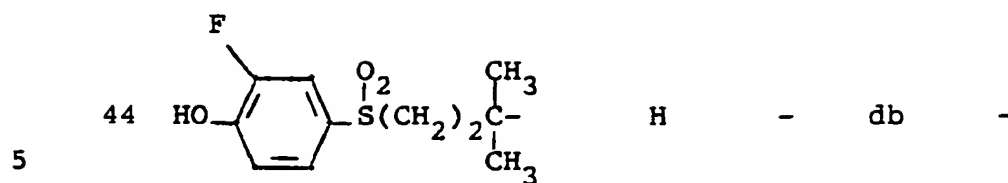
Compound	T	T ₁	b	c	d
40		CH ₃	db	-	db
41		CH ₃	db	-	-
42		H	db	-	db
43		CH ₃	-	-	-

30

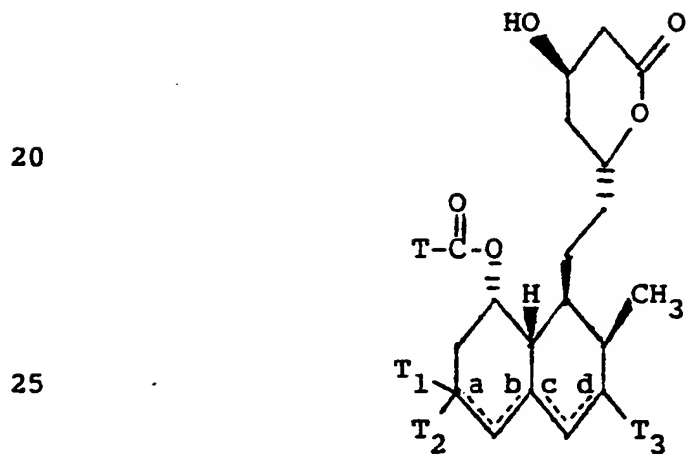
2212S/0985A

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17377Y



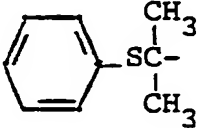
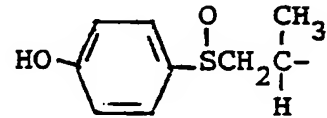
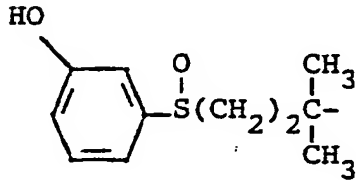
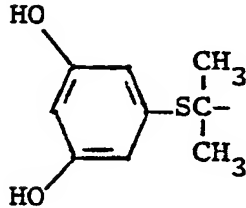
15 TABLE 9



2212S/0985A

- 60 -

17377Y

	Compound	T	T				a			
			T ₁	T ₂	T ₃		a	b	c	d
5	46		OH	H	H	-	db	-	db	
10	47		OH	H	H	-	db	-	db	
15	48		-	CH3	OH	db	-	db	-	
20	49		OH	H	H	-	-	-	-	-

30 db = double bond

EXAMPLE 50Preparation of Alkali and Alkaline Earth Salts of Compound II

To a solution of the lactone from Example 1(d) (42 mg) in ethanol (2 ml) is added aqueous NaOH (1 equivalent). After one hour at room temperature, the mixture is taken to dryness in vacuo to yield the sodium salt of Compound II.

In like manner the potassium salt is prepared using one equivalent of potassium hydroxide, and the calcium salt using one equivalent of CaO.

EXAMPLE 51Preparation of Methyl Ester of Compound II

To a solution of 400 mg of the lactone from Example 1(d) in 100 ml of absolute methanol is added 10 ml 0.1 M sodium methoxide in absolute methanol. This solution is allowed to stand at room temperature for one hour, is then diluted with water and extracted twice with ethyl acetate; the ethyl acetate, dried over anhydrous sodium sulfate, is removed in vacuo to yield the methyl ester of Compound II.

In like manner, by the use of equivalent amounts of propanol, butanol, isobutanol, t-butanol, amyl alcohol, isoamyl alcohol, 2-dimethylamino-ethanol, benzyl alcohol, phenethanol, 2-acetamido-ethanol, and the like, the corresponding esters are obtained.

EXAMPLE 52Preparation of free Hydroxy Acids

The sodium salt of the compound II from Example 50 is redissolved in 2 ml of ethanol-water (1:1) and added to 10 ml of 1N hydrochloric acid from which the hydroxy acid is extracted with ethyl acetate. The latter solvent is washed once with water, dried, and removed in vacuo with a bath temperature not exceeding 30°C. The hydroxy acid derived slowly reverts to the lactone on standing.

EXAMPLE 53

As a specific embodiment of a composition of this invention, 20 mg of the lactone from Example 1(d) is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

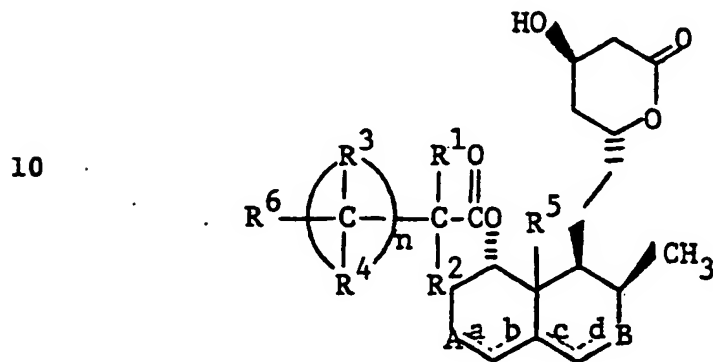
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WHAT IS CLAIMED IS:

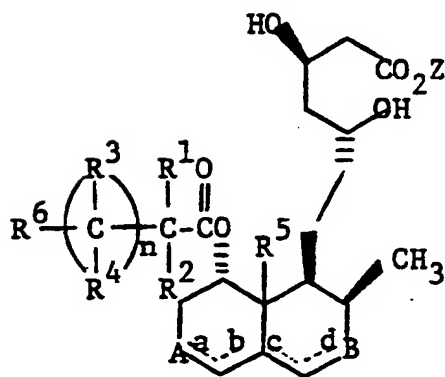
1. A compound represented by the following
 5 general structural formulae (I) or (II):



15

20

25



30 wherein:

- n is 0 to 5;
 R¹ is C₁₋₃ alkyl;
 R² is hydrogen or C₁₋₃ alkyl;

R^3 and R^4 independently are hydrogen, C_{1-3} alkyl, C_{3-7} cycloalkyl, phenyl or substituted phenyl in which the substituents are X and Y and when n is 2 to 5, each of the R^3 s and R^4 s are independently hydrogen, C_{1-3} alkyl, C_{3-7} cycloalkyl or only one of the R^3 s and R^4 s are phenyl or substituted phenyl;

R^5 is hydrogen or hydroxy;
 10 R^6 is selected from the group consisting of

- a) $R^{15} \overset{\text{O}}{\parallel} \text{OC}$ in which R^{15} is hydrogen or C_{1-3} alkyl,
- 15 b) $R^{16} R^{17} \overset{\text{O}}{\parallel} \text{NC}$ in which R^{16} and R^{17} independently are hydrogen or C_{1-3} alkyl or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a heterocycle
- 20 selected from piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or thiomorpholinyl, and

- 25 c) $R^{18} \overset{(\text{O})}{\underset{|}{\text{S}}}^q$ in which q is 0 to 2 and R^{18} is hydrogen, C_{1-5} alkyl, phenyl, and substituted phenyl wherein the substituents are X and Y;

A is $R^7 \overset{|}{\underset{\text{CH}_3}{\text{C}}}$ or $R^7 \overset{|}{\underset{|}{\text{CH}}}$ in which R^7 is hydrogen or hydroxy;

30

B is ---CHR^8 in which R^8 is hydrogen or hydroxy;
and

a, b, c and d represent single bonds, one of a, b, c,
or d represents a double bond, or both a and
5 c or both b and d represent double bonds
provided that when a is a double bond, A is
 $\text{CH}_3\text{---C=}$ or CH= and when d is a double bond B is
 =CH ; and

10 X and Y independently are hydrogen, halogen,
trifluoromethyl, C_{1-3} alkyl, nitro, cyano
or a group selected from:

a) $R^9\text{O}(\text{CH}_2)_m$ in which m is 0 to 3
and R^9 is hydrogen, C_{1-3} alkyl or
15 hydroxy- C_{1-3} alkyl;

b) $R^{10}\overset{\text{O}}{\parallel}\text{CO}(\text{CH}_2)_m$ or $R^{10}\overset{\text{O}}{\parallel}\text{OCO}(\text{CH}_2)_m$ in which
 R^{10} is hydrogen, C_{1-3} alkyl,
hydroxy- C_{2-3} alkyl, phenyl, naphthyl,
20 amino- C_{1-3} alkyl, C_{1-3} alkylamino-
 C_{1-3} alkyl, di(C_{1-3} alkyl)amino-
 C_{1-3} alkyl, hydroxy- C_{2-3} alkylamino-
 C_{1-3} alkyl or di(hydroxy- C_{2-3}
alkyl)amino- C_{1-3} alkyl;

25 c) $R^{11}\overset{\text{O}}{\parallel}\text{OC}(\text{CH}_2)_m$ in which R^{11} is hydrogen,
 C_{1-3} alkyl, hydroxy- C_{1-3} alkyl,
 C_{1-3} alkoxy- C_{1-3} alkyl, phenyl or
naphthyl;

30 d) $R^{12}R^{13}\text{N}(\text{CH}_2)_m$, $R^{12}R^{13}\overset{\text{O}}{\parallel}\text{NC}(\text{CH}_2)_m$ or
 $R^{12}R^{13}\overset{\text{O}}{\parallel}\text{NCO}(\text{CH}_2)_m$ in which R^{12} and R^{13}

- independently are hydrogen, C_{1-3} alkyl, hydroxy- C_{2-3} alkyl or together with the nitrogen atom to which they are attached form a heterocycle group selected from piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl or thio-morpholinyl;
- 5 e) $R^{14}S(O)_p(CH_2)_m$ in which p is 0 to 2 and R^{14} is hydrogen, C_{1-3} alkyl, amino, C_{1-3} alkylamino or di(C_{1-3} alkyl)-amino;
- 10 Z is hydrogen, C_{1-5} alkyl or C_{1-5} alkyl substituted with a member of the group consisting of phenyl, dimethylamino or acetylamino;
- 15 or a pharmaceutically acceptable salt of a compound of the formula (II) in which Z is hydrogen.

2. A compound according to Claim 1 wherein
- 20 R^1 is methyl;
 R^2 is methyl;
 R^3 and R^4 are hydrogen;
 R^5 is hydrogen;
 R^7 is hydrogen;
25 R^8 is hydrogen; and
a, b, c and d represent single bonds or both b and d represent double bonds.

3. A compound according to Claim 2 wherein
- 30 R^6 is $R^{15} \overset{O}{\parallel} OC$.

4. A compound according to Claim 3 which is
 6(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-3-oxo-
 propionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexa-
 hydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetra-
 5 hydro-2H-pyran-2-one;
 6(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-
 carbonylpropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a-
 (R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
 tetrahydro-2H-pyran-2-one; or the corresponding free
 10 hydroxy acid thereof.

5. A compound according to Claim 2 wherein

$$R^6 \text{ is } R^{16}R^{17}\overset{\text{O}}{\underset{\text{NC}}{\parallel}}$$

15

6. A compound according to Claim 5 which is
 6-(R)-[2-[8(S)-[3-(diethylamino)-2,2-dimethyl-
 3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
 hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
 20 tetrahydro-2H-pyran-2-one;
 6-(R)-[2-[8(S)-(2,2-dimethyl-3-morpholino-3-
 oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
 hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
 tetrahydro-2H-pyran-2-one;
 25 6-(R)-[2-[8(S)-[3-(dimethylamino)-2,2-
 dimethyl-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,-
 7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
 3,4,5,6-tetrahydro-2H-pyran-2-one;
 6-(R)-[2-[8(S)-[4-(dimethylamino)-2,2-
 30 dimethyl-4-oxobutanoyloxy)-2(S),6(R)-dimethyl-1,2,6,-
 7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
 3,4,5,6-tetrahydro-2H-pyran-2-one;

6-(R)-[2-[8(S)-[2,2-(dimethyl)-3-(methyl-
amino)-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,-
8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
3,4,5,6-tetrahydro-2H-pyran-2-one; or the
5 corresponding free hydroxy acids.

7. A compound according to Claim 2 wherein
R⁶ is R¹⁸^(O)_S^q.

10

8. A compound according to Claim 7 which is
6(R)-[2-[8(S)-[2-methyl-2-(methylthio)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
15 tetrahydro-2H-pyran-2-one.

6(R)-[2-[8(S)-[2-methyl-2-(methylsulfinyl)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one.

20 6(R)-[2-[8(S)-[2-methyl-2-(methylsulfonyl)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one.

25 6(R)-[2-[8(S)-[2-methyl-2-(phenylthio)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one.

30 6(R)-[2-[8(S)-[2-methyl-2-(phenylsulfinyl)-
propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-
tetrahydro-2H-pyran-2-one; or the corresponding free
hydroxy acid thereof.

9. A hypocholesterolic, hypolipidemic pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

5

10. A composition according to Claim 9 wherein the therapeutically active ingredient is

6-(R)-[2-[8(S)-(2,2-dimethyl-3-methoxy-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
10 hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

6-(R)-[2-[8(S)-[3-(dimethyl-3-methoxy-carbonylpropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
15 3,4,5,6-tetrahydro-2H-pyran-2-one;

6-(R)-[2-[8(S)-[3-(diethylamino)-2,2-dimethyl-3-oxo-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-
hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

20 6-(R)-[2-[8(S)-(2,2-dimethyl-3-morpholino-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;

6-(R)-[2-[8(S)-[3-(dimethylamino)-2,2-dimethyl-3-oxopropionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
25 3,4,5,6-tetrahydro-2H-pyran-2-one;

6-(R)-[2-[8(S)-[4-(dimethylamino)-2,2-dimethyl-4-oxobutanoyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-
30 3,4,5,6-tetrahydro-2H-pyran-2-one;

- 6-(R)-[2-[8(S)-[4-(dimethyl)-3-(methylamino)-3-oxopropionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 5 6-(R)-[2-[8(S)-(2-methyl-2-(methylthio)-propionyloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 10 6-(R)-[2-[8(S)-[2-methyl-2-(methylsulfinyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 15 6-(R)-[2-[8(S)-[2-methyl-2-(methylsulfonyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 20 6-(R)-[2-[8(S)-[2-methyl-2-(phenylthio)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one;
- 25 6-(R)-[2-[8(S)-[2-methyl-2-(phenylsulfinyl)-propionyloxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one; or the corresponding free hydroxy acid thereof.

